Original Paper

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2005;137:249–257
DOI: 10.1159/000086338

Received: August 30, 2004
Accepted after revision: March 2, 2005
Published online: June 16, 2005

Prevalence of Allergy Symptoms and Total IgE in a New York City Cohort and Their Association with Birth Order

Inge F. Goldstein[a, b] Matthew S. Perzanowski[a, c] Cynthia Lendor[a, e]
Robin S. Garfinkel[a, d] Lori A. Hoepner[a, d] Ginger L. Chew[a, c]
Frederica P. Perera[a, c] Rachel L. Miller[a, e]

[a]Columbia's Children's Center for Environmental Health (CCCEH), [b]Department of Epidemiology, [c]Department of Environmental Health Science, and [d]Data Coordinating Center, Mailman School of Public Health, and [e]Division of Pulmonary, Allergy, Critical Care Medicine, College of Physicians and Surgeons, Department of Medicine, Columbia University, New York, N.Y., USA

Key Words
Asthma · Wheeze · Atopy · IgE · Birth order · Hygiene hypothesis

Abstract
Background: An inverse association between birth order and allergic disease has been widely observed, but has not been examined in the high asthma prevalence, inner-city populations of the United States. As part of an ongoing prospective birth cohort study, the prevalence of early phenotypes of asthma and/or allergy was compared with those reported in other studies, and the association with birth order was evaluated. ***Methods:*** Children of Dominican and African-American mothers living in Northern Manhattan underwent detailed periodic questionnaires. Total IgE from the mothers (n = 321) and the children at birth (n = 291) and at ages 24 (n = 244) and 36 (n = 155) months was measured. The association between birth order and allergy symptoms was evaluated at 12 (n = 350), 24 (n = 290) and 36 (n = 247) months. ***Results:*** Total serum IgE was detectable (>0.5 IU/ml) in 35% of the children's cord blood and averaged 15 and 21 IU/ml at ages 24 and 36 months, respectively. They were not significantly different at any age between children with and without older siblings. Additionally, at these ages, there were no consistent associations between birth order and either wheeze, itchy eyes or eczema. ***Conclusions:*** Despite a substantially higher prevalence of asthma in the Northern Manhattan community compared with other areas, total IgE levels at ages 24 and 36 months, but not cord blood, are similar to those reported in other areas of the world. In this community, results at this age do not support a protective effect of higher birth order.

Introduction

Low-income inner-city minority populations in the United States are reported to have one of the highest prevalences of asthma morbidity and mortality in the world [1]. In this population, the high prevalence of this disease stands in contrast to the globally observed phenomenon of a higher prevalence of asthma in wealthier as compared with poorer communities [2–4]. Given the lack of a clear understanding of the high prevalence of asthma in the inner city, documenting the development of allergy and asthma in this community and comparing markers of the

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Accessible online at:
www.karger.com/iaa

Correspondence to: Dr. Inge F. Goldstein
Department of Epidemiology, Mailman School of Public Health, Columbia University
722W 168th Street, Room 735
New York, NY 10032 (USA)
Tel. +1 212 305 7660, Fax +1 212 305 9413, E-Mail ifg2@columbia.edu

appearance of these phenotypes with populations around the world could contribute to understanding the global asthma epidemic.

Despite the high burden of disease, some of the prevailing theories for the increase in asthma, specifically the 'hygiene hypothesis', have not yet been investigated in these communities. The 'hygiene hypothesis' suggests that increased hygienic practices of 20th Century Western lifestyle, including reduced exposure to bacteria and viruses early in life, are contributing factors to the increase in allergic disease seen in the last century [5]. This hypothesis was first proposed by Strachan [6] to explain the inverse association he observed between allergic rhinitis and the number of siblings living in the house when the individual was young.

An inverse birth order effect on both atopy and, to a somewhat lesser extent, on asthma has been reported in numerous studies worldwide [5–7]. In 2002, Karmaus and Botezan [7] reviewed the literature and reported that out of 31 studies reporting on the effect of sibship size on asthma and wheezing, 22 (18 of them statistically significant) reported a negative association with odds ratios (ORs) ranging from 0.2 to 0.84. In addition, they listed 11 studies that reported an association between reduced incidence of eczema in the first year of life as well as allergen-specific sensitization at age 4 with increasing sibship. The authors estimated that whatever the causal factors for the 'sibling effect' in children measured at various ages are it might be responsible for more than 30% of all cases of eczema, allergic rhinitis and asthma. Strachan [5], in discussing the effect of birth order and socioeconomic factors on atopy and asthma, assessed that those factors, taken individually or in combination, could only account for a small proportion of the observed doubling of prevalence of those conditions in a 12-year study period (1958 and 1972 birth cohorts in the United Kingdom).

The high incidence of asthma in our Northern Manhattan community and other low-income minority inner-city communities in the United States cannot be explained by the current prevailing interpretations of the hygiene hypothesis. The higher incidence of asthma and allergies in higher social classes around the world is thought to be caused by factors associated with their higher standards of hygiene [5, 6]. The higher incidence of the disease in our low-income, low socioeconomic status inner-city community cannot be ascribed to any known higher hygienic standards, and thus, together with other similar inner city communities in the US, poses a challenge to the hygiene hypothesis as it currently stands.

In this paper, we will describe the prevalence of various early phenotypes of allergic disease, including total IgE, allergic symptoms and wheeze found in a cohort of inner-city New York children in the first 3 years of life and compare it with those reported in other populations around the world, where generally a lower prevalence of asthma has been reported. The influence of birth order and the sibling effect on the development of early markers of allergy in the first 3 years will also be addressed [5, 7]. These comparisons will subsequently be discussed in terms of the 'hygiene hypothesis' and other hypotheses attempting to explain the development of asthma, and whether or how these hypotheses might specifically apply to inner-city minority populations in the US.

Materials and Methods

Study Cohort

Children were enrolled as part of a prospective birth cohort study of lower-income African-American and Dominican mothers and their children living in Northern Manhattan and the South Bronx. The study is being conducted by the Columbia Children's Center for Environmental Health, and enrollment has been described previously [8, 9]. Briefly, pregnant nonsmoking women were recruited to participate in the study through various sources in the Bronx and Northern Manhattan, including prenatal clinics, WICC (Women, Infant and Children office) flyers and referrals. The study cohort was restricted to women aged 18–35 who identified themselves as African-American or Dominican and had resided in Northern Manhattan (central Harlem or Washington Heights) or the South Bronx for at least 1 year before pregnancy. Additional exclusion factors included the use of any tobacco products during pregnancy as well as the use of illicit drugs or diagnosis of hypertension, diabetes or HIV infection, or having had their first prenatal visit after the twentieth week of pregnancy.

Participation included periodic administration of detailed questionnaires, blood collection from the mother and the child, as well as assessment of environmental exposures including allergens (cockroach, mouse and dust mites), endotoxin and air pollutants. Enrollment is ongoing, and to date, 616 mothers have been enrolled. For the analyses in this paper, measurements of total serum IgE were available from 321 of the mothers, 291 cord blood samples from the infants, 244 of the children at 24 months and 155 of the children at 36 months. Allergy-specific IgE data will be reported in a later communication. Because of some missed participation at different time points and an enrollment period of several years, the specific participants at the different ages vary, with 144 and 83 of the children in the cord blood group also being assessed at ages 24 and 36 months, respectively. There were 137 children who had IgE measured both at 24 and 36 months. A larger number of children were available for the analysis of allergic symptoms (tables 1, 3).

Questionnaire

A detailed questionnaire including asthma and allergic disease outcomes and risk factors was administered prenatally and at 12,

Table 1. Prevalence (%) of eczema, runny nose or itchy eyes and wheeze at ages 12, 24 and 36 months

	12 months			24 months			36 months		
	male	female	total	male	female	total	male	female	total
Doctor-diagnosed eczema	20 (32/162)	17 (31/188)	18 (63/350)	22 (29/130)	21 (33/160)	21 (62/290)	22 (26/118)	24 (32/133)	23 (58/251)
Runny nose or itchy eyes without a cold (in last 3 months)[1]	29 (48/190)	24 (46/190)	26 (94/356)	25 (33/132)	19 (31/163)	22 (64/295)	24 (28/119)	25 (33/34)	24 (61/253)
Wheeze (in last 3 months)[2]	24 (40/165)	17 (33/190)	21 (73/355)	20 (26/129)	12 (19/161)	16 (45/290)	16 (19/117)	8.5 (11/130)	12 (30/247)

There were no significant differences ($p > 0.05$) in the prevalence of any of the outcomes between boys and girls (χ^2).

[1] Mother reported that the child had had a runny nose or itchy eyes not associated with a cold in the 3 months prior to administration of the questionnaire.

[2] Mother reported that the child had wheezed in the 3 months prior to the questionnaire.

Table 2. Percentage of children with cord blood total IgE greater than thresholds reported in the literature

Study population[1]	n	Threshold IU/ml	Children above threshold %	Children in Northern Manhattan cohort above threshold, % (n = 275)	p value
South Africa					
Haus et al. [27], 1990	109	0.5	23	35	0.02
Denmark					
Hansen et al. [28], 1992	2,814	0.5	13	35	<0.001
Tucson, Arizona					
Guerra et al. [19], 2004	380	0.5	18.4	35	<0.001
Detroit					
Carter et al. [29], 2003	841	0.56	17	35	<0.001
German cities					
Bergmann et al. [23], 1996	6,401	0.9	8.5	23	<0.001
Sweden					
Croner et al. [30], 1986	1,652	0.9	12	23	<0.001
Brussels					
Magnusson [20], 1988	199	1.2	19	17	0.57

[1] The study population consisted of different ethnicities, but the prevalence of children with total IgE above 0.5 IU/ml was similar in each group.

24 and 36 months, with additional less detailed health follow-ups every 6 months. Data about the children obtained from the 12-, 24- and 36-month questionnaires included a report of (1) doctor-diagnosed eczema, (2) runny nose or itchy eyes without a cold (in the 3 months prior to the questionnaire) and (3) wheeze (in the 3 months prior to the questionnaire). Birth order was defined as the number of older siblings to whom the mother had given live birth. Overall, 46, 30, 16 and 8% of the children were first, second, third and fourth or higher in birth order, respectively. Premature birth was defined as a gestational age of less than 36 weeks. A question about the child spending time outside of the home every week (e.g., day care, babysitter) was included in the multivariate analysis as a surrogate for exposure to other children outside of the home.

IgE Measurement

Blood was collected from the mother and from cord blood at the time of the child's birth, and again from the child at ages 24 and 36 months. Total serum IgE was measured using an immunoradiometric assay (Total IgE IRMA, Diagnostic Products Corp., Los Angeles, Calif., USA). The lower limit of detection was 0.5 IU IgE/ml. Six of the cord blood samples were considered outliers and were excluded from the analysis (>50 IU/ml, >4 standard deviations

Table 3. Association between high total IgE at 36 months (highest quartile, >126 IU/ml) and early asthma symptoms

	n for analysis	Adjusted OR[1]
12 months		
Doctor-diagnosed eczema	140	2.1 (0.81–5.3)
Runny nose/itchy eyes without cold	142	1.1 (0.44–2.8)
Wheeze in last 3 months	141	2.8 (1.1–7.1)
24 months		
Doctor-diagnosed eczema	134	1.4 (0.52–4.0)
Runny nose/itchy eyes without cold	138	3.2 (1.1–9.4)
Wheeze in last 3 months	134	3.4 (1.2–9.8)
36 months		
Doctor-diagnosed eczema	139	0.86 (0.31–2.4)
Runny nose/itchy eyes without cold	140	5.0 (1.9–13)
Wheeze in last 3 months	135	3.3 (0.97–11)

Figures in parentheses as 95% confidence interval.

[1] Adjusted OR (95% CI) for outcome if the child has total IgE in the highest quartile at the age of 36 months. ORs were calculated with logistic regression. All of the corrected OR models included the following variables: gender, cigarette smoke exposure in the home and the mother's age. Additionally, 'wheeze in the last 3 months' was corrected for the mother reporting asthma, which was a significant risk factor for wheeze at 24 (p = 0.006) and 36 months (p = 0.04).

from geometric mean). These children did not appear to differ from the rest of the children with respect to the other measured variables. For the multivariate analysis in tables 3 and 4, the highest quartiles of total IgE in this cohort were defined as having >0.8, ≥37, ≥51 and ≥124 IU/ml for the cord blood, at 24 months, at 36 months and for the mother's samples, respectively.

Statistics

Total IgE values were log transformed with values below the limit of detection assigned half the limit of detection, and means were compared using a t test. Prevalence of symptoms was compared using the χ^2 test. The association of total IgE concentrations at different ages was computed by Pearson's correlation coefficient using log-transformed data. This test was also utilized with log-transformed IgE concentrations to assess the association between the mother's age and total IgE. Logistic regression was used to evaluate associations between high total IgE (highest quartile) and symptoms. All ORs were corrected for gender, ethnicity and exposure to tobacco smoke at home. Additionally, ORs for wheezing were corrected for the mother's report of asthma.

Logistic regression models were used to determine the association between the number of siblings and the allergic outcomes. All of the corrected OR models had included the following variables: gender, cigarette smoke exposure in the home and the mother's age. Additionally, 'wheeze in the last 3 months' was corrected for the mother's reported asthma. The variables preterm birth, mother's total IgE, mother reporting that the child spent time out of the home (i.e. daycare) and season of questionnaire administration were initially included in the multivariate analysis. However, none of these variables affected the models or were significantly associated with any of the dependent or independent variables. Because of this and the smaller number of children for whom this information was available, they were removed from the analyses.

Results

Early Allergic Symptoms

Wheeze in the 3 months prior to administration of the questionnaire was more common, although not significantly, among boys at the interviews at 24 (p = 0.051) and 36 (p = 0.062) months (table 1). Significantly, more mothers of African-American ethnicity had reported that their child had been diagnosed with eczema by a physician than mothers of Dominican ethnicity at the follow-up assessments at 12 months (28 vs. 10%, p < 0.001), 24 months (32 vs. 11%, p < 0.001) and 36 months (33 vs. 14%, p = 0.006). This difference in reported eczema between the two ethnic groups in spite of their similar IgE levels (see below) is currently under investigation. One possible explanation is a difference in the interpretation of the question by non-English-speaking mothers in spite of the fact that questionnaires are administered in both English and Spanish. No significant differences between the two ethnic groups in reports of runny nose or itchy eyes without a cold or wheeze were found at any of these ages.

Total IgE

The geometric means (95% confidence interval) of the total IgE in this cohort were 47.1 IU/ml (40–55) in the mother's serum and 15.4 IU/ml (13–18) and 23.5 IU/ml (19–29) in the children's sera at ages 24 and 36 months, respectively, comparable with levels observed in the German multicenter study with medians of 15 and 20 IU/ml at ages 2 and 3, respectively [10]. Levels of cord blood IgE from the children in this cohort were compared with those reported in the literature from other studies around the world (table 2). Generally, our study population had significantly higher levels of cord blood IgE. In our study population, no significant differences between the two ethnic groups (African-Americans and Hispanics) in concentrations of total IgE were found for the mothers or children at any age.

The mother's total IgE was moderately predictive of cord blood IgE (Pearson's r = 0.16, p = 0.013, n = 253) but not of IgE at 24 months (r = 0.14, p = 0.10, n = 144) or at 36 months (r = 0.13, p = 0.26, n = 79). Total IgE in

Table 4. Risk associated with higher birth order (1 or more older siblings) for elevated total IgE, eczema and wheeze at 12, 24 and 36 months of age

	n for analysis	OR[1]	
		uncorrected	corrected[1]
Birth			
Elevated total IgE in cord blood (highest quartile)	256	1.4 (0.78–2.4)	1.6 (0.83–3.0)
12 months			
Doctor-diagnosed eczema	350	0.59 (0.34–1.03)	0.64 (0.34–1.2)
Runny nose/itchy eyes without cold	356	1.6 (0.99–2.6)	1.5 (0.85–2.5)
Wheeze in last 3 months	355	0.98 (0.58–1.6)	1.3 (0.71–2.3)
24 months			
Elevated total IgE (highest quartile)	219	0.59 (0.32–1.1)	0.49 (0.24–0.98)
Doctor-diagnosed eczema	290	0.81 (0.46–1.4)	0.80 (0.42–1.5)
Runny nose/itchy eyes without cold	295	1.03 (0.59–1.8)	0.93 (0.50–1.7)
Wheeze in last 3 months	290	0.75 (0.39–1.4)	0.86 (0.41–1.8)
36 months			
Elevated total IgE (highest quartile)	142	1.1 (0.52–2.5)	0.72 (0.29–1.8)
Doctor-diagnosed eczema	251	1.03 (0.57–1.8)	0.90 (0.50–1.6)
Runny nose/itchy eyes without cold	253	1.3 (0.73–2.3)	0.94 (0.49–1.8)
Wheeze in last 3 months	247	0.74 (0.34–1.6)	0.61 (0.25–1.5)

Figures in parentheses as 95% confidence interval.

[1] OR (95% CI) for the outcome if the child has 1 or more older siblings. ORs were calculated with logistic regression. All of the corrected OR models had included the following variables: gender, cigarette smoke exposure in the home and the mother's age. Additionally, 'wheeze in the last 3 months' was corrected for the mother reporting asthma.

the cord blood showed an association with total IgE at 24 months ($r = 0.28$, $p = 0.001$, $n = 144$; fig. 2a) and at 36 months ($r = 0.21$, $p = 0.054$, $n = 83$). There was a strong association between total IgE at 24 and 36 months ($r = 0.74$, $p < 0.001$, $n = 137$; fig. 2b).

Total IgE and Symptoms

Elevated cord total IgE (highest quartile) and high total IgE at age 24 months were not significantly associated with any of the symptoms examined in this paper at ages 12, 24 or 36 months (adjusted OR, logistic regression). By contrast, those 36-month-old children with total IgE in the highest quartile were significantly more likely to wheeze or have itchy eyes/runny nose without a cold at age 36 months (table 3). These children were also more likely to have wheezed at 12 and 24 months. Tests for strongyloides stercoralis-specific IgG in a subset of the cohort with the highest IgE at age 24 months were all negative. This latter finding suggests that parasites are unlikely to be a major contributing factor to the total IgE levels measured in our cohort.

Associations with Birth Order

No significant differences in total IgE at birth, 24 months or 36 months between first-born children and those born later were found (fig. 1). In addition, there was no significant difference in the total IgE of the mothers for whom this was their first birth (geometric mean 47 IU/ml, range 37–58 IU/ml) compared with those who had given birth to other children (mean 47 IU/ml, range 37–60 IU/ml). An absence of significant difference in means of the mother's total IgE was also observed when the data were stratified by mothers with four or more children versus those with fewer. No association was found between the mother's age and her total IgE ($r = –0.042$, $p = 0.5$).

Multivariate analyses of the associations with birth order are reported (table 4), with birth order defined as one or more older siblings. Similar results were observed when the data were analyzed as three or more older siblings. There were no consistent associations between birth order and markers of allergic disease in the first 3 years of life. While having at least one older sibling was signif-

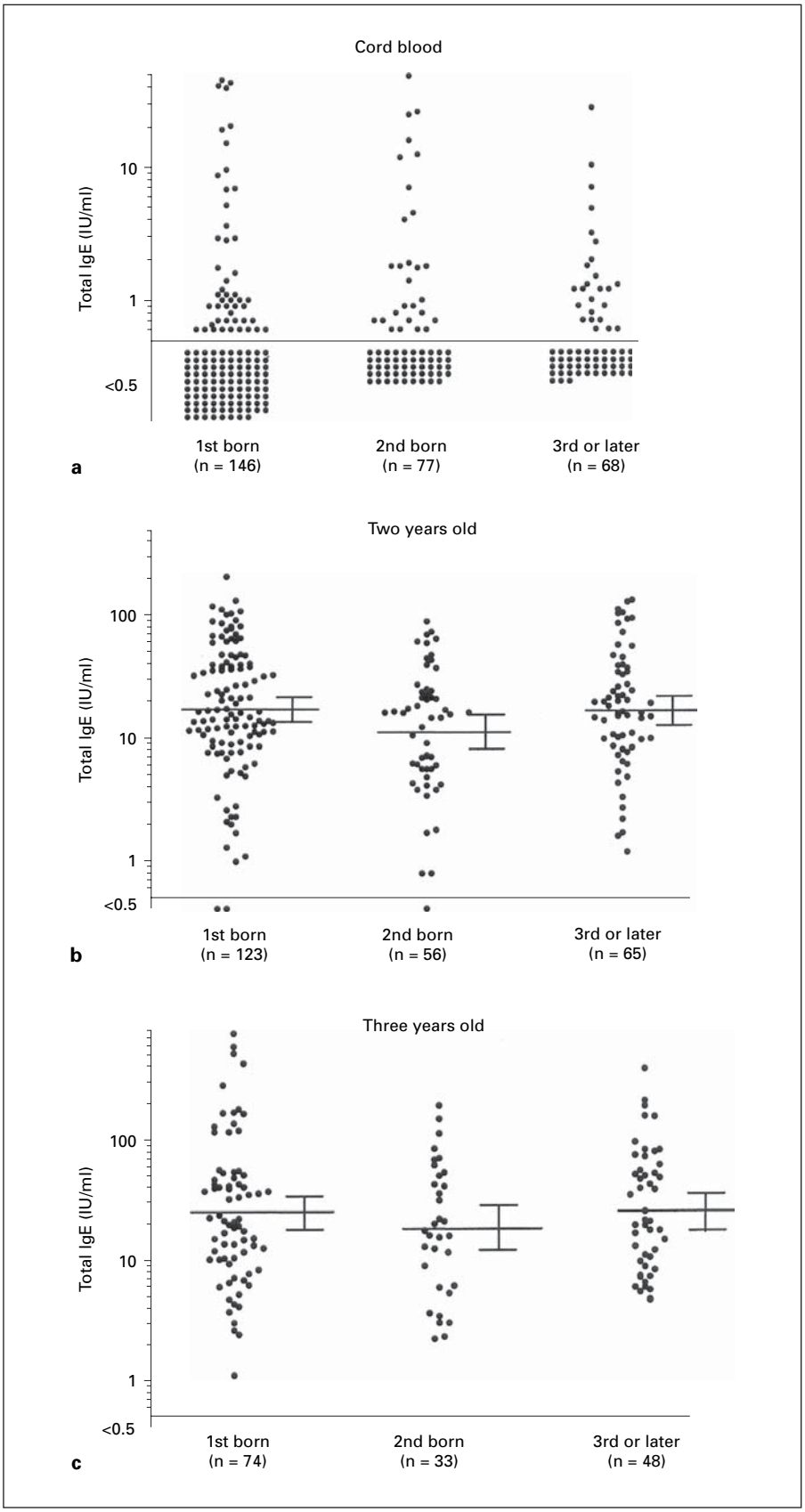

Fig. 1. Distribution of total serum IgE (IU/ml) stratified by children's birth order: cord blood (**a**), 24 months (**b**) and 36 months (**c**). **b**, **c** Long bars represent the geometric mean, shorter bars represent the 95% confidence interval of the mean. For all three ages, there were no significant differences in the geometric means of total IgE between any of the three birth order groups.

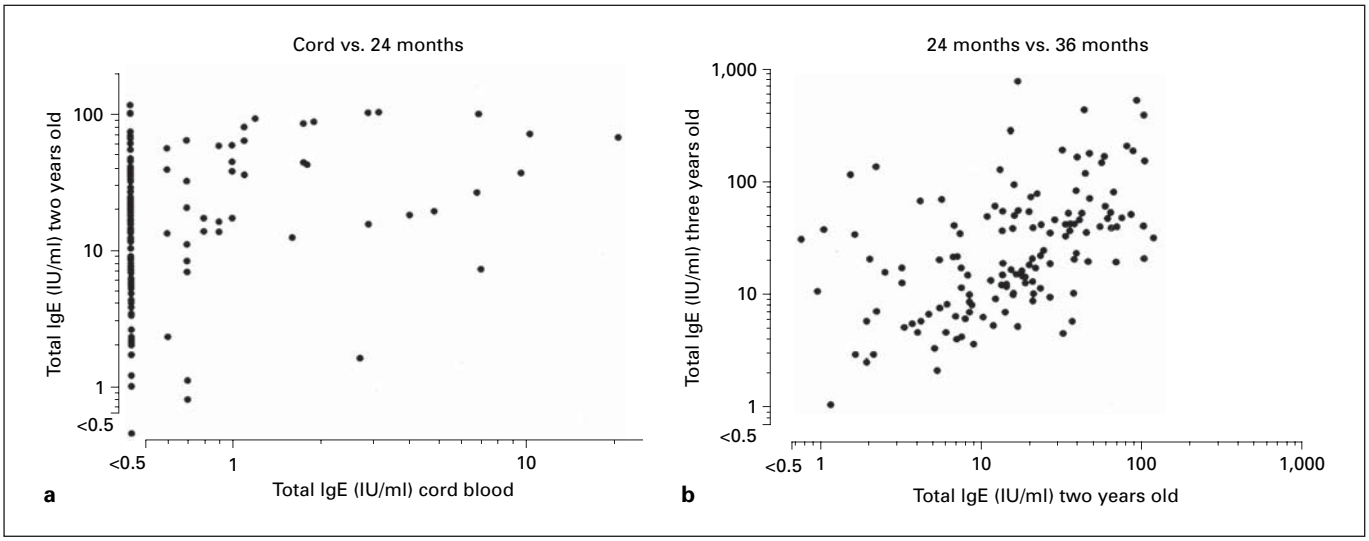

Fig. 2. Associations between total serum IgE (IU/ml) at different ages. **a** The correlation between cord blood total IgE and IgE at 24 months was r = 0.26, p = 0.003 (Pearson's correlation of log concentrations). There were 2 children with total IgE below the limit of detection in both their cord and 24-month serum samples. **b** The correlation between IgE at 24 and 36 months was r = 0.73, $p < 0.001$.

icantly negatively associated with total IgE at age 24 months (p = 0.045), a positive association (nonsignificant) was observed when the children were 1 year older (p = 0.5).

Discussion

The effect of birth order and/or sibship size as well as day-care attendance at an early age on development of atopy and asthma have been attributed to factors associated with the 'hygiene hypothesis', i.e. a protective effect of early exposure to infections that are introduced into the home by older siblings or during early attendance at day care on the subsequent development of atopy and/or asthma. This explanation has not been universally accepted. Other hypotheses, for example, have implicated in utero events or exposures as responsible for the birth order effect [11]. Supporting this position are numerous studies that demonstrate maternal compared with paternal transmission of asthma [12]. Karmaus and Botezan [7] also reported that maternal IgE decreased with increasing birth order, supporting the possibility of an in utero effect of factors associated with birth order. However, to date, mechanistic data explaining these effects have been lacking. Others have reported a decrease in maternal atopy with each successive pregnancy, which subsequently reduced the offspring's chances of developing asthma [13–15]. Karmaus et al. [16] found this effect to be strongest among atopic mothers. Gibbs et al. [17] reported in a case control study that increased exposure to infection did not protect children from atopic dermatitis, in spite of a strong birth order effect.

In addition to questions regarding possible mechanisms for the reported birth order effect, uncertainties regarding its relevance to an inner-city population need to be elucidated. Our birth cohort is derived from an inner-city low-income minority population residing in New York City with one of the highest pediatric hospitalization rates for asthma, as well as asthma prevalence, in the United States [18]. The cohort provides a unique opportunity both to begin answering these questions and to examine other attributes of the population that have often been associated with the later diagnosis of asthma. However, in contrast to reports from other regions in the world, we did not find a statistically significant birth order effect in total IgE at birth or in IgE and any of the symptoms eczema, runny nose, itchy eyes without a cold and wheeze at the early ages of 12, 24 and 36 months (table 4). Statistically significant difference in the geometric means of IgE between first, second, third or later-born children were absent (fig. 2).

The absence of a detectable birth order effect in our study population could be due to other overriding social

and/or environmental exposures in this inner-city population that mask a birth order effect, if it is present at all, at this early age. Another explanation is that the birth order effect does not present at this early age. Guerra et al. [19] reported in a birth cohort study in Tucson, Arizona, that children who had two or more siblings or who attended day care during the first 6 months of life had a lower prevalence of frequent wheeze. However, this protective effect of birth order only emerged at age 5–6 years with an OR of 0.3 by age 13. At age 2, the OR was 1.4. Many of the studies that reported a birth order effect investigated older children. Additional difficulties of assessing the birth order effect may arise from the fact that previous investigations, as well as ours, have been cross-sectional. For such an effect, a within-family determination should produce a more valid assessment.

Comparing the prevalence of early phenotypes that are often associated with asthma in our cohort with those reported in other populations, often with lower prevalence of asthma, might contribute to the understanding of the development of the disease in our population and possibly point to causes for the high rates. The percentage of children in our inner-city population with cord blood IgE above various thresholds was higher than the corresponding percentages reported in various studies around the world, with the exception of those reported by Magnusson et al. [20] (table 2). This finding may suggest that our children experience increased susceptibility to intrauterine factors (e.g., T helper 2, IL-4 or IL-13, cytokine production, allergen exposure, maternal lifestyles) suspected of increasing isotype class switching to IgE in utero [21]. But in general, the independent predictive value of cord blood IgE for risk of allergy or asthma remains unconvincing in most [22–24], but not all [25, 26], studies. Our results in the inner-city population do not support an association between increased cord blood IgE and increased risk of early respiratory disease including asthma, possibly diminishing its clinical importance. In addition, median levels of total IgE found in 2- and 3-year-old children from Germany (cohort of 4,000 children) were very similar to those from children of the same ages in our inner-city birth cohort.

Our inner-city birth cohort (through 36 months of age) does not appear to have significantly different levels of early markers of allergic diseases from those for other cohorts reported in the literature. In contrast to these reports based on very geographically disparate populations that found a birth order effect on early markers for asthma and/or atopy, we have not found such an effect so far. We are continuing to prospectively follow our New York City birth cohort and will be able to test for a birth order effect that could very well emerge later on, particularly when this cohort reaches school age, the age when a firmer diagnosis of asthma can be first made, and the age at which many studies found a birth order effect.

Acknowledgements

The authors would like to thank the participating mothers and children. This work would not have been possible without the hard work and dedication of the field technicians. Financial support was provided by the National Institute of Environmental Health Sciences (NIEHS; P50 ES09600, 5 RO1 ES08977, RO1ES111158, RO1 ES012468), the US Environmental Protection Agency (EPA; R827027, 8260901), the Irving General Clinical Research Center (RR00645), the Gladys & Roland Harriman Foundation, the Hansen Foundation, the W. Alton Jones Foundation, the New York Community Trust, the Educational Foundation of America, the Rockefeller Financial Services, the Horace W. Goldsmith Foundation, the Beldon Fund, the National Center on Minority and Health Disparities, the John Merck Fund and the New York Community Trust.

References

1 Grant EN, Daugherty SR, Moy JN, Nelson SG, Piorkowski JM, Weiss KB: Prevalence and burden of illness for asthma and related symptoms among kindergartners in Chicago public schools. Ann Allergy Asthma Immunol 1999; 83:113–120.

2 Woolcock AJ, Peat JK: Evidence for the increase in asthma worldwide. Ciba Found Symp 1997;206:122–134; discussion 34–39, 57–59.

3 Addo Yobo EO, Custovic A, Taggart SC, Asafo-Agyei AP, Woodcock A: Exercise induced bronchospasm in Ghana: Differences in prevalence between urban and rural schoolchildren. Thorax 1997;52:161–165.

4 Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 1998; 351:1225–1232.

5 Strachan DP: Family size, infection and atopy: The first decade of the 'hygiene hypothesis'. Thorax 2000;55(suppl 1):S2–S10.

6 Strachan DP: Hay fever, hygiene, and household size. BMJ 1989;299:1259–1260.

7 Karmaus W, Botezan C: Does a higher number of siblings protect against the development of allergy and asthma? A review. J Epidemiol Community Health 2002;56:209–217.

8 Miller RL, Chew GL, Bell CA, Biedermann SA, Aggarwal M, Kinney PL, Tsai WY, Whyatt RM, Perera FP, Ford JG: Prenatal exposure, maternal sensitization, and sensitization in utero to indoor allergens in an inner-city cohort. Am J Respir Crit Care Med 2001;164: 995–1001.

9 Meyer IH, Whyatt RM, Perera FP, Ford JG: Risk for asthma in 1-year-old infants residing in New York City high-risk neighborhoods. J Asthma 2003;40:545–550.

10 Kulig M, Tacke U, Forster J, Edenharter G, Bergmann R, Lau S, Wahn V, Zepp F, Wahn U: Serum IgE levels during the first 6 years of life. J Pediatr 1999;134:453–458.

11 Jones CA, Holloway JA, Warner JO: Does atopic disease start in foetal life? Allergy 2000; 55:2–10.

12 von Mutius E: The influence of birth order on the expression of atopy in families: A gene environment interaction? Clin Exp Allergy 1998; 28:1454–1456.

13 Rangaraj S, Doull I: Hormones not hygiene? Birth order and atopy. Clin Exp Allergy 2003; 33:277–278.

14 Doull IJ: Does pregnancy prevent atopy? Clin Exp Allergy 2001;31:1335–1337.

15 Sunyer J, Anto JM, Harris J, Torrent M, Vall O, Cullinan P, Newman-Taylor A: Maternal atopy and parity. Clin Exp Allergy 2001;31: 1352–1355.

16 Karmaus W, Arshad SH, Sadeghnejad A, Twiselton R: Does maternal immunoglobulin E decrease with increasing order of live offspring? Investigation into maternal immune tolerance. Clin Exp Allergy 2004;34:853–859.

17 Gibbs S, Surridge H, Adamson R, Cohen B, Bentham G, Reading R: Atopic dermatitis and the hygiene hypothesis: A case-control study. Int J Epidemiol 2004;33:199–207.

18 Garg R, Karpati A (eds): Asthma Facts, ed 2. New York, New York City Department of Health and Mental Hygiene, 2003.

19 Guerra S, Lohman IC, Halonen M, Martinez FD, Wright AL: Reduced interferon gamma production and soluble CD14 levels in early life predict recurrent wheezing by 1 year of age. Am J Respir Crit Care Med 2004;169:70–76.

20 Magnusson CG: Cord serum IgE in relation to family history and as predictor of atopic disease in early infancy. Allergy 1988;43:241–251.

21 Karmaus W, Arshad H, Mattes J: Does the sibling effect have its origin in utero? Investigating birth order, cord blood immunoglobulin E concentration, and allergic sensitization at age 4 years. Am J Epidemiol 2001;154:909–915.

22 Lilja G, Oman H: Prediction of atopic disease in infancy by determination of immunological parameters: IgE, IgE- and IgG-antibodies to food allergens, skin prick tests and T-lymphocyte subsets. Pediatr Allergy Immunol 1991;2: 6–13.

23 Bergmann RL, Edenharter G, Bergmann KE, Guggenmoos-Holzmann I, Forster J, Bauer CP, Wahn V, Zepp F, Wahn U: Predictability of early atopy by cord blood-IgE and parental history. Clin Exp Allergy 1997;27:752–760.

24 Ruiz RG, Richards D, Kemeny DM, Price JF: Neonatal IgE: A poor screen for atopic disease. Clin Exp Allergy 1991;21:467–472.

25 Businco L, Marchetti F, Pellegrini G, Perlini R: Predictive value of cord blood IgE levels in 'at-risk' newborn babies and influence of type of feeding. Clin Allergy 1983;13:503–508.

26 Michel FB, Bousquet J, Greillier P, Robinet-Levy M, Coulomb Y: Comparison of cord blood immunoglobulin E concentrations and maternal allergy for the prediction of atopic diseases in infancy. J Allergy Clin Immunol 1980;65:422–430.

27 Haus M, Heese HD, Weinberg EG, Potter PC, Malherbe D, Hall JM: Genetic and environmental influences on cord blood serum IgE and on atopic sensitisation in infancy. S Afr Med J 1990;77:7–13.

28 Hansen LG, Host A, Halken S, Holmskov A, Husby S, Lassen LB, Storm K, Osterballe O: Cord blood IgE. 1. IgE screening in 2814 newborn children. Allergy 1992;47:391–396.

29 Carter PM, Peterson EL, Ownby DR, Zoratti EM, Johnson CC: Relationship of house-dust mite allergen exposure in children's bedrooms in infancy to bronchial hyperresponsiveness and asthma diagnosis by age 6 to 7. Ann Allergy Asthma Immunol 2003;90:41–44.

30 Croner S, Kjellman NI: Predictors of atopic disease: Cord blood IgE and month of birth. Allergy 1986;41:68–70.